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ART UNIT	**PAPER NUMBER**
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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
09/392,822	Yu et al
Examiner	**Group Art Unit**
Gai (Jennifer) Mi Lee	1632

☐ Responsive to communication(s) filed on _____

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claim

☒ Claim(s) 1-28 is/are pending in the applicat

Of the above, claim(s) _____ is/are withdrawn from consideration

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) 1-28 is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☒ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☒ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____

☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☒ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

Claim Objections

Claim 18 is objected to because of the following informalities: The claim is written with two "a a TRE". Appropriate correction is required.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-28 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-32 of U.S. Patent # 5,871,726.

Although the conflicting claims are not identical, they are not patentably distinct from each other because the instantly claimed invention fully encompasses claims 1-32 of U.S. Patent #

5,871,726.

They are not patentably distinct because the claims of the instant application and the claims of U.S. Patent # 5,871,726 are overlapping, and thereby, obvious subject matter. The instant claims are drawn to the same methods that encompassed suppressing tumor growth and similar composition of a replicating recombinant adenovirus with modifications of the adenovirus vector comprising an adenovirus gene or transgene under transcriptional control element (TRE) wherein the broad claim of the instant application encompasses prostate cell specific (cell type-specific TRE) as claimed in U.S. Patent # 5,871,726. The claims of U.S. Patent # 5,871,726 are a species of the current instant application drawn to an adenovirus vector comprising an adenovirus gene essential for propagation under transcriptional control of a prostate specific response element, said prostate cell specific response element comprising an enhancer specific for prostate specific antigen and a promoter specifically. The adenoviruses of U.S. Patent # 5,871,726 encompass only relative to prostate specific response element in adenovirus vector while the instant invention claims a broader scope to an adenovirus vector comprising an adenovirus gene under any and all transcriptional control of a transcriptional regulatory element (i.e. enhancers, promoters, etc.) wherein it is a cell status-specific TRE.

However, the composition and method steps are similar and obviously anticipated in the U.S. Patent # 5,871,726. Thus, it would have been obvious to one of ordinary skilled in the art, at the time of the instant invention to apply the method of suppressing tumor growth or conferring selective cytotoxicity by the administration of a recombinant adenovirus under transcriptional

control of a transcriptional regulatory element stated above by the method steps claimed in U.S. Patent # 5,871,726.

Accordingly, the claimed processes in the patent and the present application are obvious variants.

Therefore, the inventions as claimed are co-extensive.

This is a provisional obviousness-type double patenting rejection.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 27-28 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of conferring selective cytotoxicity with direct administration of adenovirus or suppressing tumor growth with direct administration of adenovirus comprising E1A under transcriptional control of a hypoxia responsive element and a PSA-TRE, does not reasonably provide enablement for any and all cell statue-specific TRE in an adenovirus delivery system in any and all types of cells by any and all methods of administration. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The claims are directed to gene therapy delivery by a method of adenovirus administration comprising an adenovirus gene under the transcriptional regulatory element (TRE) comprising a cell status-specific TRE for conferring selective cytotoxicity on a target cell or suppressing tumor growth.

The specification discloses an adenovirus vectors comprises a cell status-specific TRE which is functional in a cell which exhibits a particular physiological characteristic which is reversible and/or progressive (p. 10). The specification further discloses that the adenoviral constructs in which the first and second cell status-specific TREs are identical or substantially identical, particularly if these TREs control transcription of early genes, may display an instability which may be desirable in certain contexts, such as when an automatic "self-destruction" property can shut down the virus, thereby controlling the degree of propagation (25). The Example on pages 48-49, teaches an adenovirus vector comprising E1A under transcriptional control of a hypoxia responsive element and a PSA-TRE *in vitro* with no guidance, working examples, or correlation to a method of conferring cytotoxicity nor a method of suppressing tumor.

With regards to extrapolating from *in vitro* data of the specification to gene therapy of a disease, the importance of relevant animal models for support of enablement is imperative in the determination for effectiveness of gene therapy. This observation is supported by Orkin et al. in the "Report and Recommendations of the Panel to Assess the NIH Investment in Research on Gene Therapy" (see pages 10-11 and 14). On page 11, second and third paragraphs, Orkin et al

emphasize the importance of relevant animal models, and state that many "mouse models often do not faithfully mimic the relevant human conditions." Orkin et al also indicated that when dealing with cancer, the relevance of animal models appears to be less predictive than with other single-gene disorders. Note that the expression levels have not been demonstrated with regard to rendering treatment to a model for cancer. Diseases and/or disorders such as tumor require that the therapeutic gene be targeted to specific cells and/or tissues in order to achieve a therapeutic result. The specification fails to teach any specific parameters or conditions under which cell targeting can be predictably achieved. Yet, Orkin et al supports and discusses that cell targeting methodologies have not reached clinical application and that research in these areas within the context of gene therapy strategies is in its infancy. See page 8, last paragraph and paragraph bridging pages 9-10. Miller et al. (The FASEB Journal, 1995) review the types of vectors available for *in vivo* gene delivery and conclude that, "for the long-term success as well as the widespread applicability of human gene therapy, there will have to be advances...targeting strategies outlined in this review, which are currently only at the experimental level, will have to be translated into components of safe and highly efficient delivery systems" (page 198, column 1). Moreover, Ledley (Pharmaceutical Research, 13: 1595-1614, 1996) states that the effectiveness of gene delivery *in vivo* is poorly predicted by *in vitro* results. Reasons why *in vitro* results would not be recapitulated *in vivo* include various biological barriers that are not reflected in *in vitro* models, and interactions between DNA or formulated DNA complexes with serum and blood elements (see page 1603, right column). In the instant application, the specification

provides no teachings on parameters for which vectors can be targeted to which cells. Therefore, even if the specification enabled the construction of the gene delivery vehicle targeted to *in vitro* cellular modification, in the absence of particular guidance, the artisan would have been required to develop *in vivo* means of practicing the claimed methods; such unpredictable gene delivery art would have been considered to have necessitated undue experimentation on the part of the practitioner.

Furthermore, Eck & Wilson (The Pharmacological Basis of Therapeutics, 1996) support the importance of tailoring a gene therapy vector and method to specific diseases and/or disorders and not to all diseases and disorders. For example, Eck & Wilson et al review the state of the art for gene therapy for inherited disorders and discloses that "[t]he level of protein function necessary to achieve complementation of the defect varies widely among genetic diseases." In particular, Eck & Wilson disclose that CFTR gene expression necessary to achieve therapeutic benefit is not known and the excessive production of an unregulated gene encoding α or β-chain of hemoglobin may result in more harm to the host than the disease itself (see page 78, column 2, Inherited Disorders). At best, the results from *in vitro* data would illustrate that direct, selective infection of the adenovirus comprising TRE can be achieved but it is not correlative nor predictive of the adenovirus effect *in vivo*.

With respect to enablement of claims directed to gene therapy or treatment, as this is an unpredictable art, a clear correlation to achieving therapeutic expression as broadly claimed must be provided by the specification. With regard to *in vivo* gene expression, Eck & Wilson go on to

report that numerous factors complicate *in vivo* gene therapy with respect to predictably achieving levels and duration of gene expression which have not been shown to be overcome by routine experimentation. These include, the fate of the DNA vector itself (volume distribution, rate of clearance into the tissues, *etc.*), the *in vivo* consequences of altered gene expression and protein function, the fraction of vector taken up by the target cell population, the trafficking of the genetic material within cellular organelles, the rate of degradation of the DNA, the level of mRNA produced, the stability of the mRNA produced, the amount and stability of the protein produced, and the protein's compartmentalization within the cell, or its secretory fate, once produced. See page 82, column 1, first paragraph. These factors differ dramatically based on the route of administration of the vector, the protein being produced, and the disease and/or host being treated. As such, the specification fails to provide guidance for any of the above parameters for *in vivo* gene expression nor do they provide a clear correlation to carrying out methods for therapeutic gene transfer protocols as broadly claimed.

Thus, the cited prior and post-filing art clearly indicates an unpredictable status of the gene therapy art. And, although, specific vectors, promoters, genes, and routes of administration might be or may have been effective for treatment of a specific disease providing a specific therapeutic effect, gene therapy as a broad-based art is clearly unpredictable in terms of achieving levels and duration of expression of a gene of interest which results in a therapeutic effect.

The claims are extremely broad, encompassing any and all routes of administration of an adenoviral vector comprising any and all adenovirus gene under the transcriptional control of a

transcriptional regulatory element(TRE) comprising a cell statue-specific TRE in any and all host, and achieving "treatment" via gene therapy of a method of suppressing any and all types of tumor growth. The courts have stated that reasonable correlation must exist between scope of a right to exclude a patent application and scope of enablement set forth in patent application. 27USPQ2d 1662 *Ex parte Maizel*. Scope of Enablement is considered in view of the Wands factors (MPEP 2164.01 (a)). In view of the quantity of experimentation necessary, the lack of direction or guidance provided by the specification, the absence of working examples for the demonstration or correlation of an adenoviral vector delivery of cell status-specific TRE to treating tumors as claimed, the unpredictable state of the art with respect to the expression of gene transfer, stability of mRNA, targeting capabilities and breadth of the claims to a method of treating by any and all routes of administration of an adenoviral vector comprising any and all adenovirus gene under the transcriptional control of a transcriptional regulatory element(TRE) comprising a cell statue-specific TRE, and achieving "treatment" via gene therapy of a method of suppressing any and all types of tumor growth, it would have required undue experimentation for one skilled in the art to make and/or use the claimed inventions as broadly claimed.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 1 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 is vague and indefinite in its recitation of "TRE comprising a cell status-specific TRE" because it is unclear what factors are encompassed within the claim to determine whether TRE comprises a cell status-specific TRE within the sequence, multiple TRE connected side by side, or TRE wherein said TRE is a cell status-specific TRE. The metes and bounds of the claim cannot be determined.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

Claims 1-3, 5-8, 11, 14, 18-20 and 23-28 are rejected under 35 U.S.C. 102(e) as being anticipated by Hallenbeck et al (U. S. Patent #5,998,205).

Hallenbeck et al disclose a targeted gene therapy using recombinant vectors and particularly adenovirus vectors that are able to selectively replicate in a target tissue to provide a

therapeutic benefit from the presence of the vector per se or from heterologous gene products expressed from the vector and distributed throughout the tissue (abstract). Hallenbeck et al further disclose that in such vectors, a gene essential for replication is placed under the control of a heterologous tissue-specific transcriptional regulatory sequence and thus, replication is conditioned on the presence of a factor(s) that induces transcription or the absence of a factor(s) that inhibits transcription of the gene by means of the transcriptional regulatory sequence with this vector, therefore, a target tissue can be selectively treated (abstract). Hallenbeck et al teach a tissue-specific replication-conditional adenovirus vector comprising: a heterologous tissue-specific transcriptional regulatory sequence operably linked to the coding region of a gene that is essential for the replication of said vector, wherein said coding region is selected from the group consisting of E1a, E1b, and E2 and E4 coding regions (see claim 1). Hallenbeck et al further teach a producer cell lines for recovering the vector or virion from the cells (column 5) wherein the E1a or E1b gene is operably linked to the tissue-specific transcriptional regulatory sequence and further encodes heterologous gene product which is expressed from the vector replicating in the target tissue (column 5). Hallenbeck et al disclose a method of treating wherein the heterologous gene product is toxic for the target tissue and where it acts on a non-toxic prodrug, converting the non-toxic prodrug into a form that is toxic for the target tissue and wherein the toxin has anti-tumor activity or eliminates cell proliferation (column 6). Hallenbeck et al disclose tissue specificity and that various combinations of transcriptional regulatory sequences can be included in a vector, thus, one or more may have the tissue-specificity in which genes are

individually (separately) controlled, however, more than one transcriptional regulatory sequence can be used if more than one such gene is desired to control replication (column 9). Thus, Hallenbeck et al clearly anticipated claims 1-3, 5-8, 11, 14, 18-20 and 23-28 of the instant invention.

Claims 1-8, 11, 14-20 and 23-27 are rejected under 35 U.S.C. 102(e) as being anticipated by Henderson et al (U.S. Patent #5,871,726).

Henderson et al disclose a host specific adenovirus vehicles by providing for transcriptional initiating regulation dependent upon transcription factors that are only active in specific, limited cell types, virus replication will be restricted to the target cells (abstract). Henderson et al disclose adenovirus genes of interest are the early genes (E1A, E1B, E2, E3 and E4) and the late genes (L1, L2 and L3), the expression of the latter being controlled by the major late promoter(column 3-4). Henderson et al further disclose that transcriptional activation is the result of interaction between transcriptional activators bound to cis-regulatory elements, factors bound to basal transcriptional elements and the activity of transcriptional mediators, or coactivators, wherein the factors are activated through chemical modification, particularly as a result of a cellular signaling mechanism (column 4). Henderson et al teach that the cell specific response element may be used with an adenovirus gene that is essential for propagation, so that replication competence is only achievable in the target cell, and/or with a transgene for changing the phenotype of the target cell (column 4-5) wherein the cell specific response element

comprising a promoter and enhancer construct specific for prostate cells, various genetic capabilities may be introduced into prostate cells expressing prostate specific antigen (column 5). Henderson et al further teach a cell specifically dependent upon androgens, particularly in prostate cells, involves an enhancer region in humans located between nt -5322 and nt -3739, relative to the transcription start site of the prostate specific antigen (PSA) and a promoter consists of nt -540 to nt +8. Juxtaposition of the two genetic elements yields a fully functional, minimal prostate-specific enhancer promoter (PSE) (column 5-6). Henderson et al further teach the use of competent adenovirus, which is competent in particular target cells, allow for proliferation of the adenovirus in the target cells resulting in the death of the host cells and proliferation of the adenovirus to other host cells and to further ensure cytotoxicity, one may have one or more transgenes present which have cytotoxic effect (column 7). Thus, Henderson et al clearly anticipated claims 1-8, 11, 14-20 and 23-27 of the instant invention.

Claims 1 and 9 are rejected under 35 U.S.C. 102(e) as being anticipated by Webster et al (U.S. Patent #5,834,306).

Webster et al disclose methods and compositions relating to chimeric genes containing (I) a tissue-specific promoter and (ii) a hypoxia response enhancer element, both of which are operably linked to a selected gene, such as a reporter gene, therapeutic gene, or deleterious gene (abstract). Webster et al disclose that regardless of the delivery means (viral *i.e.*, adenoviral vector and non-viral *i.e.*, naked DNA delivery of constructs to cells and tissues), expression of

the gene in tissues other than the target tissue, and under conditions other than hypoxic or anoxic is preferably minimal (column 8). Webster et al further disclose that the methods includes introducing into the cell a chimeric gene containing a hypoxic response element, a therapeutic gene, and a tissue-specific promoter operably linked to the therapeutic gene to control transcription of the therapeutic gene in the cell, where the element is effective to modulate expression of the therapeutic gene (column 4). Thus, Webster et al clearly anticipated claims 1 and 9 of the instant invention.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-28 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hallenbeck et al (U.S. Patent # 5, 998,205) taken with Webster et al (U.S. Patent # 5,834, 306) and Henderson (U.S. Patent #5,871,726).

Hallenbeck et al disclose a targeted gene therapy using recombinant vectors and particularly adenovirus vectors that are able to selectively replicate in a target tissue to provide a therapeutic benefit from the presence of the vector per se or from heterologous gene products expressed from the vector and distributed throughout the tissue (abstract). Hallenbeck et al further disclose that in such vectors, a gene essential for replication is placed under the control of a heterologous tissue-specific transcriptional regulatory sequence and thus, replication is conditioned on the presence of a factor(s) that induces transcription or the absence of a factor(s) that inhibits transcription of the gene by means of the transcriptional regulatory sequence with this vector, therefore, a target tissue can be selectively treated (abstract). Hallenbeck et al teach a tissue-specific replication-conditional adenovirus vector comprising: a heterologous tissue-specific transcriptional regulatory sequence operably linked to the coding region of a gene that is essential for the replication of said vector, wherein said coding region is selected from the group consisting of E1a, E1b, and E2 and E4 coding regions (see claim 1). Hallenbeck et al further teach a producer cell lines for recovering the vector or virion from the cells (column 5) wherein the E1a or E1b gene is operably linked to the tissue-specific transcriptional regulatory sequence and further encodes heterologous gene product which is expressed from the vector replicating in

the target tissue (column 5). Hallenbeck et al disclose a method of treating wherein the heterologous gene product is toxic for the target tissue and where it acts on a non-toxic prodrug, converting the non-toxic prodrug into a form that is toxic for the target tissue and wherein the toxin has anti-tumor activity or eliminates cell proliferation (column 6). Hallenbeck et al disclose tissue specificity and that various combinations of transcriptional regulatory sequences can be included in a vector, thus, one or more may have the tissue-specificity in which genes are individually (separately) controlled, however, more than one transcriptional regulatory sequence can be used if more than one such gene is desired to control replication (column 9). Hallenbeck et al differs from the claims in that the reference fails to disclose insertion of hypoxia responsive element as the cell statue-specific TRE and wherein the cell statue-specific TRE comprises an HRE and the cell-type specific TRE is a PSA-TRE of the instant invention. However, the secondary references, Webster et al and Henderson et al, cure the deficiency. Webster et al disclose the therapeutic potential of incorporating hypoxia response enhancer element operably linked to a selected gene in targeting tissue under hypoxic conditions (i.e., tumors) and that to realize the therapeutic potential, alternative modes of delivery is needed. Webster et al disclose that regardless of the delivery means, expression of the gene in tissues other than the target tissue, and under conditions other than hypoxic or anoxic is preferably minimal (column 8). Webster et al further disclose that the methods includes introducing into the cell a chimeric gene containing a hypoxic response element, a therapeutic gene, and a tissue-specific promoter operably linked to the therapeutic gene to control transcription of the therapeutic gene in the cell,

where the element is effective to modulate expression of the therapeutic gene (column 4). Webster et al teach a chimeric gene which contains a hypoxic response element, a tissue-specific promoter heterologous to the element, and a deleterious gene wherein the promoter is operably linked to the deleterious gene, and the element is effective to modulate expression of the deleterious gene. Suitable promoters include tumor-specific promoters, such as alpha fetoprotein (AFP) promoter and deleterious genes useful in this include a viral thymidine kinase gene, such as the herpes simplex virus, HSVtk (column 4-5). Henderson et al disclose a cell specifically dependent upon androgens, particularly in prostate cells, involves an enhancer region in humans located between nt -5322 and nt -3739, relative to the transcription start site of the prostate specific antigen (PSA) and a promoter consists of nt -540 to nt +8. Juxtaposition of the two genetic elements yields a fully functional, minimal prostate-specific enhancer promoter (PSE) (column 5-6). Henderson et al further disclose the use of competent adenovirus, which is competent in particular target cells, allow for proliferation of the adenovirus in the target cells resulting in the death of the host cells and proliferation of the adenovirus to other host cells and to further ensure cytotoxicity, one may have one or more transgenes present which have cytotoxic effect (column 7). It would have been obvious to one of ordinary skill in view of the teaching of Webster et al and Henderson et al to insert cell cycle-specific element from the E2F-1 gene or a cell status-specific TRE comprises a heat-inducible element into an adenoviral vector of the instant invention.

Regarding claims 12 and 13, it would have been obvious to one of ordinary skill to substitute another TRE or cell cycle-specific element into the vector in order to control selective replication in a target tissue. Hallenbeck et al clearly suggests the desirability of various transcriptional regulatory sequences depending on the specific target tissue for replication of the adenovirus.

Accordingly, the modification of the vectors of Hallenbeck et al by substituting transcriptional regulatory element/enhancer/promoter as suggested by Webster et al and Henderson et al in order to obtain a recombinant adenoviral vector was within the ordinary skill in the art at the time the claimed invention was made. From the teachings of the references, it is apparent that one of ordinary skill would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole is *prima facie* obvious, as evidenced by the references, especially in the absence of evidence to the contrary.

Conclusion

Claims 10 and 22 are objected to as being dependent upon a rejected base claims, but would be allowable if rewritten in independent form including all of the limitations of the base claims and any intervening claims.

Claims 1-9, 11-21, and 23-28 are not allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gai (Jennifer) Mi Lee, whose telephone number is 703-306-5881. The examiner can normally be reached on Monday-Thursday from 8:30 to 5:00 (EST). The examiner can also be reached on alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jasemine Chambers, can be reached on 703-308-2035. The FAX phone numbers for group 1600 are 703-308-4242 and 703-305-3014.

An inquiry of a general nature or relating to the status of the application should be directed to the group receptionist whose telephone number is 703-308-0196.

Gai (Jennifer) Lee
Patent Examiner
Art Unit 1600

Jasemine C. Chambers

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